Docket No: BMS-2027 (r A-7176) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Shuang Liu, et al.** Confirmation No.: **5136**

Serial No.: **09/899,629** Group Art Unit: **1617**

Filing Date: **July 5, 2001** Examiner: **Shengjun Wang**

For: **Stable Radiopharmaceutical Compositions And Methods For Preparation Thereof**

Mail Stop Appeal-Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the final rejection of claims 19-22, 30-33, and 35-39 dated January 18, 2006. A Notice of Appeal was filed on May 18, 2006.

1. REAL PARTY IN INTEREST

Bristol-Myers Squibb Pharma Company by virtue of the assignment recorded on February 11, 2002, at Reel 012607, Frame 0038.

2. RELATED APPEALS AND INTERFERENCES

The Examiner's previous rejections of claims 19-22, 30-33, and 35-39 of the present application were vacated by the Board (Appeal No. 2005-2132; mailed August 30, 2005).

3. STATUS OF CLAIMS

Claim 1	Withdrawn
Claim 2	Withdrawn
Claim 3	Withdrawn
Claim 4	Withdrawn
Claim 5	Withdrawn
Claim 6	Withdrawn
Claim 7	Withdrawn
Claim 8	Withdrawn
Claim 9	Withdrawn
Claim 10	Withdrawn
Claim 11	Withdrawn
Claim 12	Withdrawn
Claim 13	Withdrawn
Claim 14	Withdrawn
Claim 15	Withdrawn
Claim 16	Withdrawn
Claim 17	Withdrawn
Claim 18	Withdrawn
Claim 19	Rejected and On Appeal
Claim 20	Rejected and On Appeal
Claim 21	Rejected and On Appeal
Claim 22	Rejected and On Appeal
Claim 23	Withdrawn
Claim 24	Withdrawn
Claim 25	Withdrawn
Claim 26	Withdrawn
Claim 27	Withdrawn
Claim 28	Withdrawn
Claim 29	Withdrawn
Claim 30	Rejected and On Appeal
Claim 31	Rejected and On Appeal
Claim 32	Rejected and On Appeal
Claim 33	Rejected and On Appeal
Claim 34	Withdrawn
Claim 35	Rejected and On Appeal
Claim 36	Rejected and On Appeal
Claim 37	Rejected and On Appeal
Claim 38	Rejected and On Appeal
Claim 39	Rejected and On Appeal
Claim 40	Withdrawn
Claim 41	Withdrawn
Claim 42	Withdrawn
Claim 43	Withdrawn
Claim 44	Withdrawn
Claim 44	Withdrawn
Claim 46	Withdrawn
Claim 47	Withdrawn
Claim 48	Withdrawn
Claim 49	Withdrawn
Claim 50	Withdrawn
Claim 51	Withdrawn
Claim 52	Withdrawn
Claim 53	Withdrawn
Claim 54	Withdrawn
Claim 55	Withdrawn
Claim 56	Withdrawn
Claim 57	Withdrawn
Claim 58	Withdrawn
Claim 59	Withdrawn
Claim 60	Withdrawn
Claim 61	Withdrawn
Claim 62	Withdrawn
Claim 63	Withdrawn
Claim 64	Withdrawn
Claim 65	Withdrawn
Claim 66	Withdrawn
Claim 67	Withdrawn
Claim 68	Withdrawn
Claim 69	Withdrawn
Claim 70	Withdrawn
Claim 71	Withdrawn
Claim 72	Withdrawn
Claim 73	Withdrawn
Claim 74	Withdrawn
Claim 75	Withdrawn
Claim 76	Withdrawn
Claim 77	Withdrawn
Claim 78	Withdrawn
Claim 79	Withdrawn
Claim 80	Withdrawn
Claim 81	Withdrawn
Claim 82	Withdrawn
Claim 83	Withdrawn
Claim 84	Withdrawn
Claim 85	Withdrawn
Claim 86	Withdrawn
Claim 87	Withdrawn
Claim 88	Withdrawn
Claim 89	Withdrawn
Claim 90	Withdrawn
Claim 91	Withdrawn
Claim 92	Withdrawn

4. STATUS OF AMENDMENTS

No amendment has been filed subsequent to the final rejection of January 18, 2006.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to stable radiopharmaceutical compositions for treating patients; such compositions are preferably administered parenterally to treat or diagnose certain conditions. *See Appellant's Specification* at pages 61-62. As claimed in Appellant's sole pending independent claim, Claim 19, the present invention conceptually comprises a **two part composition**, Formula II and Formula I.

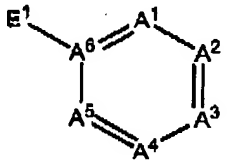
Specifically, Claim 19 recites:

A pharmaceutical composition comprising:

(1.) a radiolabeled pharmaceutical agent of the formula (II)

$$RI\text{-}Ch\text{-}L_n\text{-}(BM)_x \qquad (II);$$ and

(2.) an effective stabilizing amount of a compound of formula (I):



wherein

RI is ^{99m}Tc, ^{131}I, ^{125}I, ^{123}I, ^{117m}Sn, ^{111}In, ^{97}Ru, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{177}Lu, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{131}I, ^{32}P, ^{211}At, ^{47}Sc, ^{109}Pd, ^{105}Rh, ^{186}Re, ^{188}Re, ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu;

C_h is a metal chelator or is a direct linkage;

L_n is a linking group or is a direct linkage;

each BM is independently an antibody, an antibody fragment, a peptide, a peptidomimetic, or a non-peptide;

x is 1 to about 10;

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1;

provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with

0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 aikyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$;

or a pharmaceutically acceptable salt thereof;

provided the compound of formula (I) is not (1) a substituted monohydroxyl aromatic compound; (2) a substituted dihydroxyl aromatic compound, in which the two hydroxyl groups are not adjacent to each other; (3) a substituted monohydroxyl-monoamino aromatic compound, in which the hydroxyl group and amino group are not adjacent to each other; or (4) an ortho, meta, or para aminobenzioc acid.

In the first part, Formula II, a biological molecule (BM), such as an antibody, an antibody fragment, a peptide, a peptidomimetic, or a non-peptide, is provided for targeting the diseased tissue. This biological molecule is radio-labeled with a radionuclide (RI) (*i.e.*, radioactive atom) for having a diagnostic or therapeutic effect on the tissue. Such an arrangement results in the radioactivity being concentrated in the areas of interest, such as a tumor, as opposed to being dispersed throughout the body, which is desirable for a number of reasons, including safety and efficacy. An optional chelator (referred to variously as Ch or C_h based on a formatting tic), mainly for use with metallic radionuclides, and an optional linking group (Ln), useful to resolve steric and pharmacokinetic problems, are also provided.

The second part of the composition is a stabilizer compound, Formula I. In the industry, other stabilizing compounds, *which do not meet Formula I*, were known. *See Appellant's specification* at pages 6, line 30 - 8, line 8. Appellant's specification specifically excludes compounds like gentisic acid and derivatives thereof from Formula I. *Id.* at page 29, lines 23-31.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 under the judicially created doctrine of obviousness-type double patenting over claims 22 and 28-30 of U.S. Patent No. 6,537,520 (the Rajopadhye reference) in view of U.S. Patent No. 5,679,318 (the Vanderheyden reference) and further in view of the abstract of JP 56144060 to Nippon Oils and Fats Co. (the Yoshinaga reference).

Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 as obvious over the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Yoshinaga reference.

Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 as obvious over U.S. Patent No. 5,750,088 (the Sworin reference) in view of the Vanderheyden reference and further in view of the Yoshinaga reference.

Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 as obvious over U.S. Patent No. 5,707,603 (the Toner reference) in view of the Vanderheyden reference and further in view of the Yoshinaga reference.

7. ARGUMENT

A. Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 under the judicially created doctrine of obviousness-type double patenting over claims 22 and 28-30 of the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Yoshinaga reference.

Claim 19

Claim 19 is recited above at Section 5 and below at Section 8. The claim includes a proviso that recites: "provided the compound of formula (I) is not ... (2) a substituted dihydroxyl aromatic compound, in which the two hydroxyl groups are not adjacent to each other." The *proviso* excludes a number of compounds, *including gentisic acid*, as discussed below. **No cited reference (or combination) suggests the desirability of combining compounds of Formula I with compounds of Formula II.**

No *prima facie* case of obviousness has been made by the Examiner. The MPEP provides that:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP 706.02(j).

The Examiner admits that the Rajopadhye reference "does not expressly claims [*sic*] the stabilizers in the composition or kit." *Office Action dated January 18, 2006* at page 4. **In fact, no compounds of Formula I are taught or suggested by the Rajopadhye reference.**[1]

Likewise, the Vanderheyden reference, which discloses radionuclides, human serum, and "antioxidants such as ascorbic acid, gentisic acid, reductic acid, derivatives thereof ..."

[1] The policy concern of a double patenting rejection lies in preventing an improper extension of a patent monopoly by filing multiple applications on obvious variations of the same invention. However, by the Examiner's own admission above, this present invention cannot be an obvious variation of the Rajopadhye reference, because other references are needed to supply its lack of teachings.

fails to teach or suggest compounds of Formula I. The Examiner has failed to show that these compounds are obvious variants of Formula I. In fact, Formula I excludes all three of the compounds by structure or proviso. Thus, these compounds cannot add to a *prima facie* case of obviousness. As mentioned above, the Appellant's specification expressly teaches that gentisic acid is excluded from the invention. *Appellant's specification* at page 29, lines 23-31. Application of this reference fails to give weight to all limitations of the claims, and is improper.

The Yoshinaga reference is supplied to teach gallic acid, but it really teaches a synergistic mixture of compounds of Formula I with compounds that are excluded from Formula I - hardly sufficient for a showing of obviousness. The Derwent World Patents Index abstract states "[b]y **combining L-ascorbic acid in gallic acid,** the discolouration with iron can be prevented, and also the antioxidising activity of gallic acid **is synergically intensified**. Oxidn. of the oil and fat in feed, can be prevented."

Appellant submits that the Yoshinaga reference is not analogous art, that no suggestion or motivation exists for combining the references, and that no motivation exists to modify the reference to meet the claim.

In order to be analogous art, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). Clearly, the reference Yoshinaga reference is not in the field of Appellants' endeavor. The reference is concerned with relates to "[a]ntioxidant for feed use," more particularly, a combination of antioxidants which prevents oxidation "of the oil and fat in feed."

As the reference is not in the field of Appellant's endeavor, the case law requires that the references "be reasonably pertinent to the particular problem with which the inventor was concerned." MPEP §2141.01(a) (emphasis added). A reference is "reasonably pertinent" if "the matter with which it deals, logically would have commended itself to an inventor's

attention in considering his problem." *Id.* at §2141.01(a) (similarly, "the subject matter disclosed therein [must be] relevant to the particular problem with which the inventor is involved"). Appellant has stated that "[u]pon information and belief, the oxidation of fats and oils in feed renders the feed less palatable to cattle, swine, and the like - thus causing reduced consumption and hence, reduced weight gain. Thus, not even a similar problem is solved." *Appellant's response dated July 15, 2004.*

The Yoshinaga reference fails to teach the desirability of using gallic acid with radionuclides (the Vanderheyden reference also fails in this respect). The Examiner states (without support) that gallic acid and gentisic acid are equally suitable, but this is directly rebutted by the Appellant's specification, which specifically excludes gentisic acid, but not gallic acid.

The Examiner has ignored not just the teachings of the specification, but also the references he cited. For example, the Toner reference discloses that not all antioxidants work equally well in pharmaceuticals in the Background section, which explains that **choosing the identity of the antioxidant is critical**:

> Another problem with some prior art compositions is that the chelator must be activated by a reducing agent before forming the radionuclide chelate. If the protein conjugates are to be formed prior to formation of the radionuclide chelate, then the reducing agent employed for activating the complexing agent can degrade the protein.

Thus, the teachings of record strongly rebut the implication that antioxidants are interchangeable. The Examiner is impermissibly using hindsight based on Appellant's disclosure to state that gallic acid would be a suitable radiopharmaceutical ingredient.

Finally, even if the Examiner's antioxidant rationale is sufficient to allow the reference to be cited, it does not meet all the claim limitations. The Yoshinaga reference is limited to using ascorbic acid in gallic acid, wherein "the antioxidising activity of gallic acid is synergically intensified." The ascorbic acid must be removed to meet Appellant's claim limitation for Formula I, but the Examiner has provided no teaching that ascorbic acid is an

optional component. **To the contrary, the synergistic result requires the presence of ascorbic acid.** Since teachings and suggestions of the Yoshinaga reference clearly requires the presence of ascorbic acid, **the reference teaches away from any modification to remove the ascorbic acid.**

The combination has failed to teach or suggest the desirability of combining compounds of Formula I with compounds of Formula II. No *prima facie* case of obviousness has been made by the Examiner.

Claim 20

Claim 20 enjoys the benefits of Claim 19, with the further limitation that E^1 is OH; A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;A^5 is C(OH); each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5,C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 or aryl substituted with 0-5 R^5;R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

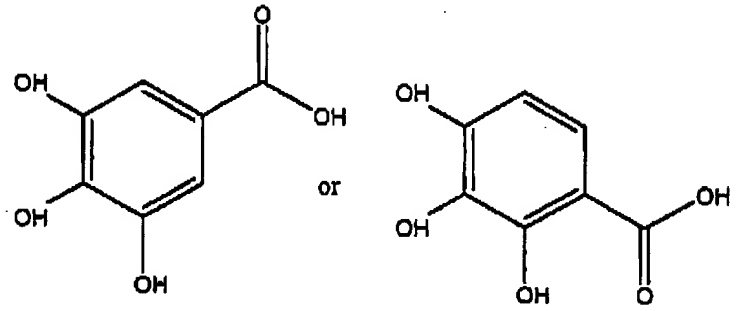
Claim 21

Claim 21 enjoys the benefits of Claim 20, with the further limitation that A^4 is C(OH); and each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has failed to make a proper *prima*

facie showing for these claims for the reasons above.

Claim 22

Claim 22 enjoys the benefits of Claim 21, with the further limitation that the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 30

Claim 30 enjoys the benefits of Claim 19, with the further limitation that the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 31

Claim 31 enjoys the benefits of Claim 19, with the further limitation that the radioisotope is present at a level of about 20 mCi to about 2000 mCi and at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 32

Claim 32 enjoys the benefits of Claim 31, with the further limitation that the radioisotope is ^{90}Y or ^{177}Lu. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 33

Claim 20 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is a peptide. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 35

Claim 35 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is a peptidomimetic. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 36

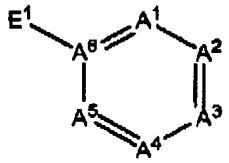
Claim 36 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is an antibody. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 37

Claim 37 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is an antibody fragment. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 38

Claim 38 enjoys the benefits of Claim 19, further comprising an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein, E^1 is NH_2 or OH; A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH; each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$ or a pharmaceutically acceptable salt thereof. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 39

Claim 39 enjoys the benefits of Claim 38, with the further limitation that the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The

Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

B. Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 as obvious over the Rajopadhye reference in view of the Vanderheyden reference and further in view of the Yoshinaga reference.

Appellant submits that the entire argument from ***Section A*** above is applicable here - no *prima facie* case of obviousness has been established due to the deficiencies of the Vanderheyden and Yoshinaga references mentioned above.

Moreover, at the time the invention of the present application was made, Application U.S. Serial No. 09/899,629 and U.S. Patent No. 6,537,520 were both owned by, or subject to an obligation of assignment to, DuPont Pharmaceuticals Company. They are now commonly owned by Bristol-Myers Squibb Pharma Company. Thus, the Rajopadhye reference is not available for 35 U.S.C. §103(a) by virtue of 35 U.S.C. §103(c). Appellant notes that it was improper to renew the rejection once the Appellant's counsel had made the above statement in the first appeal, as the MPEP provides that:

> The applicant(s) or the representative(s) of record have the best knowledge of the ownership of their application(s) and reference(s), and their statement of such is **sufficient evidence** because of their paramount obligation of candor and good faith to the USPTO.

Id at. 706.02(l)(2); emphasis added.

C. Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 as obvious over the Sworin reference in view of the Vanderheyden reference and further in view of the Yoshinaga reference.

Claim 19

The Examiner admits that the Sworin reference does "not teach expressly adding

stabilizers ...". *Office Action dated January 18, 2006* at page 8. Thus, by necessity, the Sworin reference **fails to teach any compounds of Formula I.**

Likewise, the Vanderheyden reference, which discloses radionuclides, human serum, and "antioxidants such as ascorbic acid, gentisic acid, reductic acid, derivatives thereof ..." **fails to teach or suggest compounds of Formula I.** The Examiner has failed to show that these compounds are obvious variants of Formula I. In fact, Formula I excludes all three of the compounds by structure or proviso. Thus, these compounds cannot add to a *prima facie* case of obviousness. As mentioned above, the Appellant's specification expressly teaches that gentisic acid is excluded from the invention. *Appellant's specification* at page 29, lines 23-31. Application of this reference fails to give weight to all limitations of the claims, and is improper.

The Yoshinaga reference is supplied to teach gallic acid, but it really teaches a synergistic mixture of compounds of Formula I with compounds that are excluded from Formula I - hardly sufficient for a showing of obviousness. The Derwent World Patents Index abstract states "[b]y **combining L-ascorbic acid in gallic acid**, the discolouration with iron can be prevented, and also the antioxidising activity of gallic acid is **synergically intensified**. Oxidn. of the oil and fat in feed, can be prevented."

Appellant submits that the Yoshinaga reference is not analogous art, that no suggestion or motivation exists for combining the references, and that no motivation exists to modify the reference to meet the claim.

In order to be analogous art, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). Clearly, the reference Yoshinaga reference is not in the field of Appellants' endeavor. The reference is concerned with relates to "[a]ntioxidant for feed use," more particularly, a combination of antioxidants which prevents oxidation "of the oil and fat in feed."

As the reference is not in the field of Appellant's endeavor, the case law requires that the references "be reasonably pertinent to the particular problem with which the inventor was concerned." MPEP §2141.01(a) (emphasis added). A reference is "reasonably pertinent" if "the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *Id.* at §2141.01(a) (similarly, "the subject matter disclosed therein [must be] relevant to the particular problem with which the inventor is involved"). Appellant has stated that "[u]pon information and belief, the oxidation of fats and oils in feed renders the feed less palatable to cattle, swine, and the like - thus causing reduced consumption and hence, reduced weight gain. Thus, not even a similar problem is solved." *Appellant's response dated July 15, 2004.*

The Yoshinaga reference fails to teach the desirability of using gallic acid with radionuclides (the Vanderheyden reference also fails in this respect). The Examiner states (without support) that gallic acid and gentisic acid are equally suitable, but this is directly rebutted by the Appellant's specification, which excludes gentisic acid, but not gallic acid. *The Examiner has ignored not just the teachings of the specification, but also the references he cited.* As shown above, the references rebut the implication that antioxidants are interchangeable. The Examiner is impermissibly using hindsight based on Appellant's disclosure to state that gallic acid would be a suitable radiopharmaceutical ingredient.

Finally, even if the Examiner's antioxidant rationale is sufficient to allow the reference to be cited, it does not meet the claims. The Yoshinaga reference is limited to using ascorbic acid in gallic acid, wherein "the antioxidising activity of gallic acid is synergically intensified." The ascorbic acid must be removed to meet Appellant's claim limitation for Formula I, but the Examiner has provided no teaching that ascorbic acid is an optional component. **To the contrary, the synergistic result requires the presence of ascorbic acid.** Since teachings and suggestions of the Yoshinaga reference clearly requires the presence of ascorbic acid, **the reference teaches away from any modification to remove**

the ascorbic acid.

Thus, as the combination has failed to teach or suggest the desirability of combining compounds of Formula I with compounds of Formula II, a *prima facie* case of obviousness has not been made by the Examiner.

Claim 20

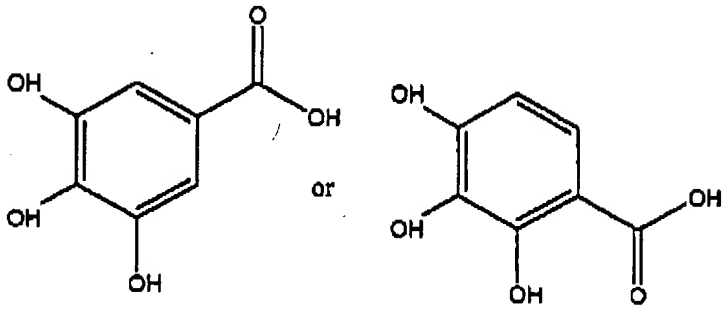
Claim 20 enjoys the benefits of Claim 19, with the further limitation that E^1 is OH; A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1; A^5 is C(OH); each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 or aryl substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 21

Claim 21 enjoys the benefits of Claim 20, with the further limitation that A^4 is C(OH); and each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 22

Claim 22 enjoys the benefits of Claim 21, with the further limitation that the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 30

Claim 30 enjoys the benefits of Claim 19, with the further limitation that the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 31

Claim 31 enjoys the benefits of Claim 19, with the further limitation that the radioisotope is present at a level of about 20 mCi to about 2000 mCi and at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 32

Claim 32 enjoys the benefits of Claim 31, with the further limitation that the radioisotope is ^{90}Y or ^{177}Lu. The Examiner has failed to make a proper *prima facie* showing

for these claims for the reasons above.

Claim 33

Claim 20 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is a peptide. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 35

Claim 35 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is a peptidomimetic. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 36

Claim 36 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is an antibody. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

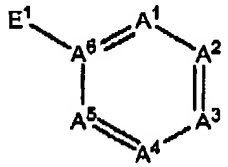
Claim 37

Claim 37 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is an antibody fragment. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 38

Claim 38 enjoys the benefits of Claim 19, further comprising an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol,

p-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein, E^1 is NH_2 or OH; A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH; each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$ or a pharmaceutically acceptable salt thereof. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 39

Claim 39 enjoys the benefits of Claim 38, with the further limitation that the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

D. Whether the Examiner has properly rejected Claims 19-22, 30-33, and 35-39 as obvious over the Toner reference in view of the Vanderheyden reference and further in view of the Yoshinaga reference.

Claim 19

The Examiner admits that the Toner reference does "not teach expressly adding stabilizers ...". *Office Action dated January 18, 2006* at page 9. Thus, by necessity, the Sworin reference **fails to teach any compounds of Formula I.**

Likewise, the Vanderheyden reference, which discloses radionuclides, human serum, and "antioxidants such as ascorbic acid, gentisic acid, reductic acid, derivatives thereof ..." **fails to teach or suggest compounds of Formula I.** The Examiner has failed to show that these compounds are obvious variants of Formula I. In fact, Formula I excludes all three of the compounds by structure or proviso. Thus, these compounds cannot add to a *prima facie* case of obviousness. As mentioned above, the Appellant's specification expressly teaches that gentisic acid is excluded from the invention. *Appellant's specification* at page 29, lines 23-31. Application of this reference fails to give weight to all limitations of the claims, and is improper.

The Yoshinaga reference is supplied to teach gallic acid, but it really teaches a synergistic mixture of compounds of Formula I with compounds that are excluded from Formula I - hardly sufficient for a showing of obviousness. The Derwent World Patents Index abstract states "[b]y **combining L-ascorbic acid in gallic acid, the discolouration with iron can be prevented, and also the antioxidising activity of gallic acid is synergically intensified.** Oxidn. of the oil and fat in feed, can be prevented."

Appellant submits that the Yoshinaga reference is not analogous art, that no suggestion or motivation exists for combining the references, and that no motivation exists to modify the reference to meet the claim.

In order to be analogous art, the reference must either be in the field of applicant's

endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). Clearly, the reference Yoshinaga reference is not in the field of Appellants' endeavor. The reference is concerned with relates to "[a]ntioxidant for feed use," more particularly, a combination of antioxidants which prevents oxidation "of the oil and fat in feed."

As the reference is not in the field of Appellant's endeavor, the case law requires that the references "be reasonably pertinent to the particular problem with which the inventor was concerned." MPEP §2141.01(a) (emphasis added). A reference is "reasonably pertinent" if "the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *Id.* at §2141.01(a) (similarly, "the subject matter disclosed therein [must be] relevant to the particular problem with which the inventor is involved"). Appellant has stated that "[u]pon information and belief, the oxidation of fats and oils in feed renders the feed less palatable to cattle, swine, and the like - thus causing reduced consumption and hence, reduced weight gain. Thus, not even a similar problem is solved." *Appellant's response dated July 15, 2004.*

The Yoshinaga reference fails to teach the desirability of using gallic acid with radionuclides (the Vanderheyden reference also fails in this respect). The Examiner states (without support) that gallic acid and gentisic acid are equally suitable, but this is directly rebutted by the Appellant's specification, which excludes gentisic acid, but not gallic acid. *The Examiner has ignored not just the teachings of the specification, but also the references he cited.* As shown above, the references rebut the implication that antioxidants are interchangeable. The Examiner is impermissibly using hindsight based on Appellant's disclosure to state that gallic acid would be a suitable radiopharmaceutical ingredient.

Finally, even if the Examiner's antioxidant rationale is sufficient to allow the reference to be cited, it does not meet the claims. The Yoshinaga reference is limited to using ascorbic acid in gallic acid, wherein "the antioxidising activity of gallic acid is synergically

intensified." The ascorbic acid must be removed to meet Appellant's claim limitation for Formula I, but the Examiner has provided no teaching that ascorbic acid is an optional component. **To the contrary, the synergistic result requires the presence of ascorbic acid.** Since teachings and suggestions of the Yoshinaga reference clearly requires the presence of ascorbic acid, **the reference teaches away from any modification to remove the ascorbic acid.**

Thus, as the combination has failed to teach or suggest the desirability of combining compounds of Formula I with compounds of Formula II, a *prima facie* case of obviousness has not been made by the Examiner.

Claim 20

Claim 20 enjoys the benefits of Claim 19, with the further limitation that E^1 is OH; A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;A^5 is C(OH); each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5,C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 or aryl substituted with 0-5 R^5;R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

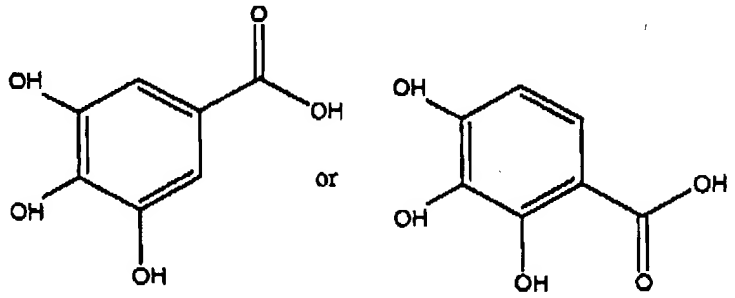
Claim 21

Claim 21 enjoys the benefits of Claim 20, with the further limitation that A^4 is C(OH);

and each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 22

Claim 22 enjoys the benefits of Claim 21, with the further limitation that the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 30

Claim 30 enjoys the benefits of Claim 19, with the further limitation that the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 31

Claim 31 enjoys the benefits of Claim 19, with the further limitation that the radioisotope is present at a level of about 20 mCi to about 2000 mCi and at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 32

Claim 32 enjoys the benefits of Claim 31, with the further limitation that the radioisotope is ^{90}Y or ^{177}Lu. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 33

Claim 20 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is a peptide. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 35

Claim 35 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is a peptidomimetic. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 36

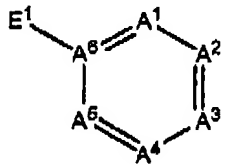
Claim 36 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is an antibody. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 37

Claim 37 enjoys the benefits of Claim 19, with the further limitation that the biomolecule is an antibody fragment. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 38

Claim 38 enjoys the benefits of Claim 19, further comprising an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (*I*):



wherein, E^1 is NH_2 or OH; A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH; each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5; R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$ or a pharmaceutically acceptable salt thereof. The Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

Claim 39

Claim 39 enjoys the benefits of Claim 38, with the further limitation that the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL. The

Examiner has failed to make a proper *prima facie* showing for these claims for the reasons above.

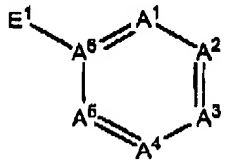
8. CLAIMS APPENDIX

1. (Withdrawn) A pharmaceutical composition comprising:

(1.) a radiolabeled pharmaceutical agent of the formula (II)

$$RI\text{-}Ch\text{-}L_n\text{-}(BM)_x \qquad (II);$$ and

(2.) an effective stabilizing amount of a compound of formula (I):



wherein

RI is ^{99m}Tc, ^{131}I, ^{125}I, ^{123}I, ^{117m}Sn, ^{111}In, ^{97}Ru, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{177}Lu, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{131}I, ^{32}P, ^{211}At, ^{47}Sc, ^{109}Pd, ^{105}Rh, ^{186}Re, ^{188}Re, ^{60}Cu, ^{62}Cu, ^{64}Cu or ^{67}Cu;

C_h is a metal chelator or is a direct linkage;

L_n is a linking group or is a direct linkage;

each BM is independently a peptidomimetic or a non-peptide;

x is 1 to about 10;

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$;

or a pharmaceutically acceptable salt thereof.

2. (Withdrawn) The composition of claim 1 wherein

E_1 is OH;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_2-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

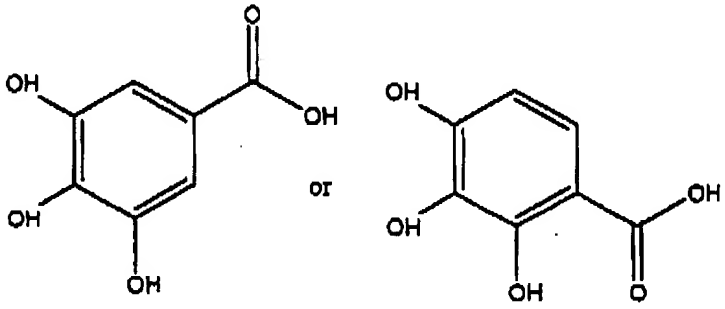
each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

3. (Withdrawn) The composition of claim 2 wherein,

A^4 is C(OH); and

each R^1 is independently C(O)H, $C(O)NH_2$, C(O)NHNH$_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

4. (Withdrawn) The composition of claim 3 wherein the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof.

5. (Withdrawn) The composition of claim 1 wherein

E^1 is NH_2;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl

substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

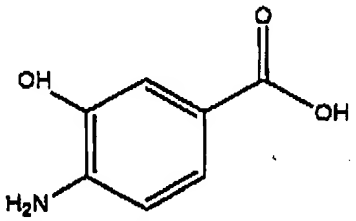
R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

6. (Withdrawn) The composition of claim 5 wherein

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

7. (Withdrawn) The composition of claim 6 wherein compound of the formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

8. (Withdrawn) The composition of claim 1 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently N, C(OH) or CR^1; provided that A^5 is not C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5 or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

9. (Withdrawn) The composition of claim 8 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently CR^1;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

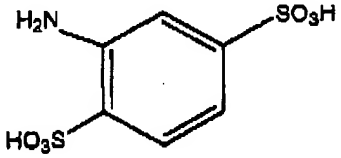
R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH; S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

10. (Withdrawn) The composition of claim 9 wherein

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

11. (Withdrawn) The composition of claim 10 wherein the compound of formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

12. (Withdrawn) The composition of claim 1 wherein the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

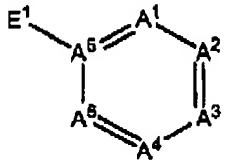
13. (Withdrawn) The composition of claim 12 wherein the radioisotope is present at a level of about 20 mCi to about 2000 mCi and is present at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition.

14. (Withdrawn) The composition of claim 13 wherein the radioisotope is ^{90}Y or ^{177}Lu.

15. (Withdrawn) The composition of claim 1 wherein the biomolecule is a peptidomimetic.

16. (Withdrawn) The composition of claim 1 wherein the biomolecule is a non-peptide.

17. (Withdrawn) The composition of claim 1 further comprising an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein,

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1;

provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C^1-C^{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$

or a pharmaceutically acceptable salt thereof.

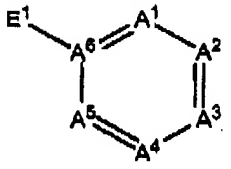
18. (Withdrawn) The composition of claim 17 wherein the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

19. (Rejected And On Appeal) A pharmaceutical composition comprising:

(1.) a radiolabeled pharmaceutical agent of the formula (II)

$$RI\text{-}Ch\text{-}L_n\text{-}(BM)_x \qquad (II);$$ and

(2.) an effective stabilizing amount of a compound of formula (I):



wherein

RI is ^{99m}Tc, ^{131}I, ^{125}I, ^{123}I, ^{117m}Sn, ^{111}In, ^{97}Ru, ^{203}Pb, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{177}Lu, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{131}I, ^{32}P, ^{211}At, ^{47}Sc, ^{109}Pd, ^{105}Rh, ^{186}Re, ^{188}Re, ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu;

C_b is a metal chelator or is a direct linkage;

L_n is a linking group or is a direct linkage;

each BM is independently an antibody, an antibody fragment, a peptide, a peptidomimetic, or a non-peptide;

x is 1 to about 10;

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1;

provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 aikyl, C_3-C_6 cycloalkyl, C_1-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl, optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, $C(=O)NHOH$, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$;

or a pharmaceutically acceptable salt thereof;

provided the compound of formula (I) is not (1) a substituted monohydroxyl aromatic compound; (2) a substituted dihydroxyl aromatic compound, in which the two hydroxyl groups are not adjacent to each other; (3) a substituted monohydroxyl-monoamino aromatic compound, in which the hydroxyl group and amino group are not adjacent to each other; or (4) an ortho, meta, or para aminobenzioc acid.

20. (Rejected And On Appeal) The composition of claim 19 wherein

E^1 is OH;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

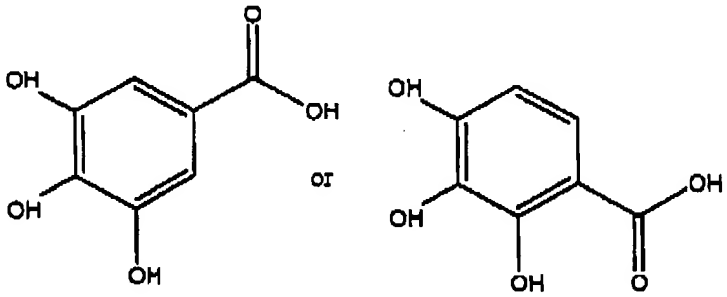
each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

21. (Rejected And On Appeal) The composition of claim 20 wherein,

A^4 is C(OH); and

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

22. (Rejected And On Appeal) The composition of claim 21 wherein the compound of formula (I) is:



or a pharmaceutically acceptable salt thereof.

23. (Withdrawn) The composition of claim 19 wherein

E^1 is NH_2;

A^1, A^2, A^3, and A^4 are each independently C(OH) or CR^1;

A^5 is C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4,

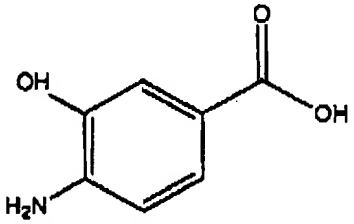
$NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1–C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

24. (Withdrawn) The composition of claim 23 wherein each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

25. (Withdrawn) The composition of claim 24 wherein compound of the formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

26. (Withdrawn) The composition of claim 19 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently N, C(OH) or CR^1; provided that A^5 is not C(OH);

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-$C_{,0}$ alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$,

$NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

27. (Withdrawn) The composition of claim 26 wherein

A^1, A^2, A^3, A^4, and A^5 are each independently CR^1

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-3 R^5, C_3-C_{10} cycloalkyl substituted with 0-3 R^5, C_2-C_{10} alkenyl substituted with 0-3 R^5, or aryl substituted with 0-5 R^5

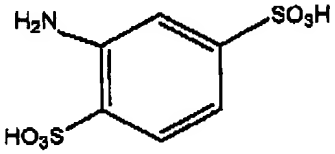
R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

28. (Withdrawn) The composition of claim 27 wherein

each R^1 is independently C(O)H, $C(O)NH_2$, $C(O)NHNH_2$, CO_2H, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$.

29. (Withdrawn) The composition of claim 28 wherein the compound of formula (I) is a compound of the formula:



or a pharmaceutically acceptable salt thereof.

30. (Rejected And On Appeal) The composition of claim 19 wherein the compound of formula (I) is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

31. (Rejected And On Appeal) The composition of claim 30 wherein the radioisotope is present at a level of about 20 mCi to about 2000 mCi and at a concentration of greater than about 5 mCi/mL of the radiopharmaceutical composition.

32. (Rejected And On Appeal) The composition of claim 31 wherein the radioisotope is ^{90}Y or ^{177}Lu.

33. (Rejected And On Appeal) The composition of claim 19 wherein the biomolecule is a peptide.

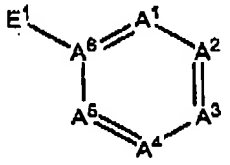
34. (Withdrawn) The composition of claim 19 wherein the biomolecule is a non-peptide.

35. (Rejected And On Appeal) The composition of claim 19 wherein the biomolecule is a peptidomimetic.

36. (Rejected And On Appeal) The composition of claim 19 wherein the biomolecule is an antibody.

37. (Rejected And On Appeal) The composition of claim 19 wherein the biomolecule is an antibody fragment.

38. (Rejected And On Appeal) The composition of claim 19 further comprising an effective stabilizing amount of a second stabilizer selected from the group consisting of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I):



wherein,

E^1 is NH_2 or OH;

A^1, A^2, A^3, A^4 and A^5 are each independently N, C(OH) or CR^1; provided at least one of A^1, A^2, A^3, A^4 and A^5 is not CH;

each R^1 is independently H, $C(O)R^2$, $C(O)OR^2$, $NHC(=O)NHR^2$, $NHC(=S)NHR^2$, $OC(=O)R^2$, $OC(=O)OR^2$, $S(O)_2OR^2$, $C(O)NR^3R^4$, $C(O)NR^3OR^4$, $C(O)NR^2NR^3R^4$, NR^3R^4, $NR^3C(O)R^4$, $PO(OR^3)(OR^4)$, $S(O)_2NR^3R^4$, $S(O)_2NR^2NR^3R^4$, $S(O)_2NR^3OR^4$, C_1-C_{10} alkyl substituted with 0-5 R^5, C_3-C_{10} cycloalkyl substituted with 0-5 R^5, C_2-C_{10} alkenyl substituted with 0-5 R^5, or aryl substituted with 0-5 R^5;

R^2, R^3, and R^4 are each independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_5 alkenyl, benzyl, or phenyl; or R^3 and R^4 together form C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl,

optionally interrupted with O, S, NH, S(=O), $S(O)_2$, P(=O)(OH), C(=O)NH, NHC(=O), NHC(=O)NH, or NHC(=S)NH; and

each R^5 is independently H, NH_2, OH, CO_2H, $C(=O)NH_2$, C(=O)NHOH, $C(=O)NHNH_2$, $NHC(=NH)NH_2$, $NHC(=O)NH_2$, $NHC(=S)NH_2$, PO_3H_2, SO_3H, or $S(O)_2NH_2$

or a pharmaceutically acceptable salt thereof.

39. (Rejected And On Appeal) The composition of claim 38 wherein the second stabilizer is present at a concentration of about 0.1 mg/mL to about 20 mg/mL.

40. (Withdrawn) A method for preparing a stable radiopharmaceutical composition of claim 1 comprising:

combining in the absence of oxygen, the radiolabeled pharmaceutical agent of the formula (II):

$$RI\text{-}Ch\text{-}L_n(BM)_x \qquad (II);$$ and

an effective stabilizing amount of the stabilizer of the formula (I).

41. (Withdrawn) The method of claim 40 wherein the radiolabeled pharmaceutical agent and the stabilizer are combined in a container.

42. (Withdrawn) The method of claim 41 wherein an oxygen free head-space is maintained in the container.

43. (Withdrawn) The method of claim 40 further comprising cooling to a temperature of less than about -20°C.

44. (Withdrawn) The method of claim 40 further comprising storing to a temperature of less than about -20°C.

45. (Withdrawn) A method for preparing a stable radiopharmaceutical composition of claim 1 comprising:

combining in a container, in the absence of oxygen, the radiolabeled pharmaceutical agent of the formula $RI\text{-}Ch\text{-}L_n\text{-}(BM)_x$ and an effective stabilizing amount of the stabilizer of the formula (I);

maintaining an oxygen free head-space in the container;

cooling the container to a temperature of less than about -20° C; and
storing the container to a temperature of less than about -20°C.

46. (Withdrawn) A method for treating or preventing thromboembolic disorders, atherosclerosis, infection, inflammation, transplant rejection, cancer or a disease state that is associated with the following receptors: a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ34, selectin, growth factor (PDGF, VEGF, BGF, FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha 5\beta 1$, $\alpha 4\beta 1$, $\alpha 1\beta 1$, or $\alpha 2\beta 2$, $\alpha 5\beta 1$, $\alpha v\beta 3$, $\alpha 5\beta 1$, or tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family in a mammalian tissue inflicted with or at risk thereof comprising contacting the mammalian tissue with an effective amount of a composition of claim 1.

47. (Withdrawn) The method of claim 46 wherein the mammal is a human.

48. (Withdrawn) The method of claim 46 wherein the contacting is *in vivo*.

49. (Withdrawn) The method of claim 46 wherein the contacting is *in vitro*.

50. (Withdrawn) A method for treating or preventing cancer,thromboembolic disorders, atherosclerosis, infection, inflammation, transplant rejection, cancer or a disease state that is associated with the following receptors: a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ4, selectin, growth factor (PDGF, VBGF, EGF, FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha 5\beta 1$, $\alpha 4\beta 1$, $\alpha 1\beta 1$, or $\alpha 2\beta 2$, $\alpha 5\beta 1$, $\alpha v\beta 3$, $\alpha 5\beta 1$ or tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family in a patient (e.g., mammal) inflicted with or at risk thereof comprising administering to the mammal in need of such treatment or prevention an effective amount of a composition of claim 1.

51. (Withdrawn) The method of claim 50 wherein the mammal is a human.

52. (Withdrawn) A method for imaging a tumor on or in a mammalian tissue inflicted with a tumor comprising contacting the mammalian tissue with an effective amount of a composition of claim 1; and detecting the presence of the radiolabeled pharmaceutical;

wherein the ligand has an affinity for tumor cells.

53. (Withdrawn) The method of claim 52 wherein the mammal is a human.

54. (Withdrawn) The method of claim 52 wherein the contacting is *in vivo*.

55. (Withdrawn) The method of claim 52 wherein the contacting is *in vitro*.

56. (Withdrawn) A method for imaging a tumor in a mammal inflicted with a tumor comprising administering to the mammal an effective amount of a composition of claim 1; and detecting the presence of the radiolabeled pharmaceutical.

57. (Withdrawn) The method of claim 56 wherein the mammal is a human.

58. (Withdrawn) The method of claim 56 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary gland, or the heart.

59. (Withdrawn) A pharmaceutical composition of claim 1 for use in medical therapy or diagnosis.

60. (Withdrawn) The use of a pharmaceutical composition of claim 1 for the manufacture of a medicament for imaging or treating a tumor in a mammal.

61. (Withdrawn) The use of a pharmaceutical composition of claim 1 for the manufacture of a medicament for treating a tumor, a thromboembolic disorder, atherosclerosis, an infection, inflammation, transplant rejection or a disease state that is associated with the following receptors: a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ4, selectin, growth factor (PDGF, VEGF, EGF, FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, αvβ3, αvβ5, α5β1, α4β1, α1β1, or α2β2, α5β1, αvβ3, α5β1or tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family in a mammal.

62. (Withdrawn) A diagnostic composition comprising an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$, an effective stabilizing amount of a compound of formula (I) of claim 1, and a physiologically acceptable carrier or excipient.

63. (Withdrawn) A compound of formula (I) of claim 1 for use in preparing a stable radio-imaging composition comprising an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$, an effective stabilizing amount of a compound of formula (I) of claim 1, and a physiologically acceptable carrier or excipient.

64. (Withdrawn) A scintigraphic diagnostic composition comprising an effective stabilizing amount of a compound of formula (I)and a radiolabeled agent RI-Ch-Ln-$(BM)_x$ of claim 1.

65. (Withdrawn) A method of *in vivo* radio-imaging comprising:

(a) introducing a radioisotope (RI) to a solution comprising a compound Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I) of claim 1, to form a labeled solution;

(b) administering the labeled solution *in vivo;* and

(c) detecting localization of the radioisotope *in vivo.*

66. (Withdrawn) A method of *in vitro* radio-imaging a targeted receptor of a tissue comprising:

(a) administering an effective diagnostic amount of a composition according to claim 62 to the tissue; and

(b) detecting localization of the radiolabeled agent at the targeted receptor.

67. (Withdrawn) The method according to claim 66 wherein the targeted receptor is selected from the group consisting of a cyclic IIb/IIIa receptor, a fibrinogen receptor, a myocardial receptor, a renal receptor, LTβ4, selectin, growth factor (PDGF, VBGF, EGF, FGF, TNF MCSF or an interleukin I11-8), a receptor that is expressed or upregulated in angiogenic tumor vasculature, αvβ3, αvβ5, α5β1, α4β1, α1β1, or α2β2, α5β1, αvβ3, α5β1 and tyrosine kinases (e.g., epidermal growth factor receptor (EGFR) family.

68. (Withdrawn) A method of radio-imaging a targeted site within a patient's body

comprising:

(a) administering an effective diagnostic amount of a composition according to claim 62 to the patient; and

(b) detecting localization of the radiolabeled agent at the targeted site.

69. (Withdrawn) A method of radio-imaging for prostate cancer or other tissues having an androgen receptor in a patient comprising:

(a) administering an effective diagnostic amount of a composition according to claim 62; and

(b) detecting the presence of the radiolabeled agent RI-Ch-Ln-$(BM)_x$ bound to the androgen receptor.

70. (Withdrawn) A method of radio-imaging metastasized cancer cells comprising contacting an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I) of claim 1, with a composition comprising ST receptor wherein said radiolabeled agent is capable of targeting a ST receptor.

71. (Withdrawn) A method of radio-imaging a patient's organ comprising:

(a) administering an effective diagnostic amount of a radiolabeled agent RI-Ch-Ln-$(BM)_x$, and an effective stabilizing amount of a compound of formula (I) of claim 1 to a patient in need of such radioimaging; and

(b) and detecting the presence of the radiolabeled agent bound to said organ.

72. (Withdrawn) The method of claim 71 wherein the organ is selected from the group consisting of the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary gland, and the heart.

73. (Withdrawn) A method of delivering a radionuclide to a target location, comprising: providing a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and providing an effective stabilizing amount of a compound of formula (I) of claim 1.

74. (Withdrawn) The method of claim 73 wherein the target location is a cancer cell.

75. (Withdrawn) A kit for preparing a radio-imaging composition, the kit comprising a sealed vial containing a predetermined quantity of a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I) of claim 1.

76. (Withdrawn) A kit comprising a plurality-vial system of a radio-imaging composition of claim 62 and a diluent, comprising:

(a) a first vial comprising a predetermined quantity of a radiolabelled agent RI-Ch-Ln-$(BM)_x$ and an effective stabilizing amount of a compound of formula (I); and

(b) a second vial comprising a pharmaceutically acceptable carrier or diluent.

77. (Withdrawn) A pharmaceutical composition comprising a radiolabeled agent RI-Ch-Ln-$(BM)_x$, an effective stabilizing amount of a compound of formula (I) of claim 1, and optionally an effective stabilizing amount of a second stabilizer compound selected from the group consisting of of ascorbic acid, benzyl alcohol, gentisic acid, an ester of gentisic acid, gentisyl alcohol, an ester of gentisyl alcohol, *p*-aminobenzoic acid, cystamine, cystamine, 5-amino-2-hydroxybenzoic acid, nicotinic acid, nicotinamide, propylene glycol, dextran, inositol, a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

78. (Withdrawn) A method of preparing a stable radiopharmaceutical composition, comprising:

providing a radiolabeled agent RI-Ch-Ln-$(BM)_x$ and providing an effective stabilizing amount of a compound of formula (I) of claim 1.

79. (Withdrawn) A method of treating cancer, comprising administering to a patient, in need thereof, a therapeutically effective amount of a pharmaceutical composition according to claim 77 and optionally at least one agent selected from the group consisting of a chemotherapeutic agent and a radio sensitizer agent, or a pharmaceutically acceptable salt thereof.

80. (Withdrawn) The method according to claim 79 wherein administering is concurrent.

81. (Withdrawn) The method according to claim 79 wherein administering is sequential.

82. (Withdrawn) The method of treating cancer according to claim 79 wherein the cancer is a vascularized tumor (i.e. a solid tumor).

83. (Withdrawn) The method according to claim 79 wherein the cancer is selected from the group consisting of carcinomas of the lung, breast, ovary, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, prostate,thyroid, squamous cell carcinomas, adenocarcinomas, small cell carcinomas, melanomas, gliomas, and neuroblastomas.

84. (Withdrawn) The method according to claim 79 wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor- 1, colony stimulating factor-2, denileukin diftitox, interleukin-2, and leutinizing hormone releasing factor.

85. (Withdrawn) The method according to claim 79 wherein the radiosensitizer agent is selected from the group consisting of 2-(3-nitro-1,2,4-triazol- 1 -yl)-N-(2-methoxyethyl)acetamide, N-(3 -nitro-4-quinolinyl)-4-morpholinecarboxamidine, 3-amino-1,2,4-benzotriazine- 1,4-dioxide, N-(2-hydroxyethyl)-2-nitroimidazole-1-acetamide, 1-(2-nitroimidazol-1-yl)-3-(1-piperidinyl)-2-propanol, and 1-(2-nitro- 1 -imidazolyl)-3-(1-aziridino)-2-propanol.

86. (Withdrawn) A kit for treating cancer, comprising a therapeutically effective amount of a pharmaceutical composition according to claim 77 and optionally at least one agent

selected from the group consisting of a chemotherapeutic agent and a radiosensitizer agent,or a pharmaceutically acceptable salt thereof.

87. (Withdrawn) The kit according to claim 86 wherein said kit comprises a plurality of separate containers, wherein at least one of said containers contains a therapeutically effective amount of a pharmaceutical composition according to claim 77, and at least another of said containers contains one or more agents selected from the group consisting of a chemotherapeutic agent and a radiosensitizer agent, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

88. (Withdrawn) The kit according to Claim 86, wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, and leutinizing hormone releasing factor.

89. (Withdrawn) The kit according to Claim 86, wherein the chemotherapeutic agent is selected from the group consisting of mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, and lisuride.

90. (Withdrawn) The kit according to Claim 86 wherein the chemotherapeutic agent is selected from the group consisting of oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, and formestane.

91. (Withdrawn) The kit according to Claim 86 wherein the chemotherapeutic agent is selected from the group consisting of interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diflitox, interleukin-2, and leutinizing hormone releasing factor.

92. (Withdrawn) The kit according to Claim 86, wherein the radiosensitizer agent is selected from the group consisting of 2-(3-nitro-1,2,4-triazol-1-yl)-N-(2-methoxyethyl)acetamide, N-(3-nitro-4-quinolinyl)-4-morpholinecarboxamidine, 3-amino-1 ,2,4-benzotriazine- 1,4-dioxide, N-(2-hydroxyethyl)-2-nitroimidazole-1 -acetamide, 1 -(2-nitroimidazol- 1 -yl)-3 - (1 -piperidinyl)-2-propanol, and 1 -(2-nitro- 1 -imidazolyl)-3-(1 -aziridino)-2-propanol.

9. EVIDENCE APPENDIX

None.

10. RELATED PROCEEDINGS APPENDIX

Appeal No. 2005-2132, in connection with the present application; mailed August 30, 2005.

Docket No: BMS-2027 (PH-7176) PATENT

11. SIGNATURE PAGE

Date: October 17, 2006

/Brian J. Hubbard/
Brian J. Hubbard
Registration No. 45,873

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439